Blazar teaches the use of inhibitors, including those that bind both B7-1 and B7-2 to induce T cell unresponsiveness for bone marrow transplantation.

The standard required for finding anticipation under 35 U.S.C. § 102(b) is stated in MPEP § 2131. "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the...claim'. *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)." Blazar does not meet this standard, and therefore, does not anticipate the claimed invention.

In our last response, we argued that Blazar did not teach contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and recipient cells from the patient from about 1 to about 48 hours before being introduced to the patient. In response, the Examiner alleges that Blazar teaches saturating B7 with "inhibitors" such as hCTLA-4Ig and anti-LFA-1 for 3 hours, and thus Blazar meets the claim limitation, "from about 1 to about 48 hours," found in independent claims 1 and 9. (Claims 2-8 depend on claim 1. Claim 10 depends on claim 9.) The Examiner concludes that claims 1-10 are thus anticipated by Blazar. The Examiner's conclusion, however, is mistaken.

The claims do not recite the limitation "inhibitors." Claims 1 and 9 recite "contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific for B7-2...from about 1 to 48 hours" (emphasis added). hCTLA-4Ig is a CTLA-4

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Ig fusion protein. It is not an immunoglobulin specific to either B7-1 or B7-2 (Blazar, Abstract). Anti-LFA-1 is also not an immunoglobulin specific to B7-1, or an immunoglobulin specific for B7-2. The anti-LFA-1 antibody specifically recognizes LFA-1, a protein distinct from B7-1 or B7-2. Instead, LFA-1 is an integrin protein that binds ICAM-1, ICAM-2 and/or ICAM-3, whereas B7-1 and B7-2 bind to CD28 and CTLA4 surface receptors on T cells. (Blazar page 7, line 23 - page 8, line 18; page 2, lines 2-8).

Blazar does not teach "contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2...for a period of time from about 1 to 48 hours." Because Blazar fails to teach every element of the claimed invention it cannot anticipate the claimed invention. Applicants respectfully request the withdrawal of this rejection.

Obviousness Rejection Under 35 U.S.C. § 103

Claims 1-10 stand rejected as being obvious in light of Blazar alone, or in combination with U.S. Patent No. 6,096,537 (hereinafter Chappel). The Examiner alleges the claimed invention is rendered obvious by Blazar because Blazar allegedly discloses a 3-hour in vitro incubation step with non-antibody B7 inhibitors and additionally discloses B7 specific antibodies administered in vivo. The Examiner further alleges the claimed invention is rendered obvious by Blazar in light of Chappel, which teaches masking antigens for 30 minutes to induce immunological non-responsiveness. Applicants submit the rejection is in error and respectfully request that it be withdrawn.

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The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The PTO has not established that the claimed invention is prima facie obvious in light of the teachings of Blazar alone. Blazar would not motivate the skilled artisan to modify its disclosure to attain the claimed invention as it actually teaches away from the present invention. Chappel adds nothing to cure this defect.

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desirability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP §2141. The Patent and Trademark Office (PTO) bears the burden of initially establishing a prima facie case of obviousness. MPEP § 2142.

Blazar

The Examiner points to the same passage in Blazar discussed above regarding anticipation to now allege that the claimed invention is obvious under 35 U.S.C. § 103.

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The Examiner alleges that a skilled artisan would have been motivated by Blazar to use the 3 hour in vitro hCTLA-4Ig and anti-LFA-1 incubation step disclosed in Blazar with the B7-1 and B7-2 specific antibodies of the claimed invention. Based on this reasoning the Examiner concludes the claimed invention is obvious. This conclusion lacks merit.

Blazar employed the 3 hour in vitro incubation period with only one B7 inhibitor, i.e. CTLA-4Ig. In various experiments it was combined with a second agent that inhibited T cell function by inhibiting pathways/mechanisms that are distinct from the B7/CD28 co-stimulatory pathway. Blazar's second agent instead focused on the IL-2 pathway or inhibition of T cell adhesion to antigen presenting cells with anti-LFA-1. In other cases, the CTLA-4Ig was administered alone. The in vitro regimen was sometimes followed with a continued in vivo dose of one or more agents. The results obtained showed the best survival rates were obtained when 2 pathways/mechanisms were targeted for disruption (e.g., the B7 costimulatory pathway and either the IL-2 pathway or the adhesion mechanism). The mice that received only CTLA-4Ig did not fare as well as the mice that were treated with two distinct agents (*See* Blazar Experiments 1-3, pages 29-31 and Figures 1, 5, and 7). Blazar, therefore, teaches that an in vitro incubation prior to transplant requires a regimen that targets at least two distinct pathways/mechanisms. Thus, Blazar teaches away from performing an in vitro incubation step targeting only one pathway. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986).

Antibodies to B7-1 and B7-2 both target the same pathway i.e. the B7/CD28 co-stimulatory pathway. A skilled artisan would thus find no motivation in Blazar to use

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B7-1 and B7-2 specific antibodies in an ex vivo regimen to induce tolerance. Blazar does not teach why this regimen would be desirable. The claimed invention therefore cannot be obvious in light of Blazar alone.

Additionally, the skilled artisan would have no reasonable expectation of success in attempting the claimed method based on Blazar. Blazar teaches in vitro targeting of the co-stimulatory pathway alone (e.g. with CTLA-Ig) is not as effective as in vitro targeting the co-stimulatory pathway in conjunction with a second pathway/mechanism. (*See* Blazar p. 31-32). Blazar, thus, teaches the importance of targeting two pathways when using an ex vivo pre-incubation step. Therefore, nothing in Blazar suggests the ex vivo targeting of the B7 pathway alone would be successful. Thus, the claimed invention is not obvious in light of Blazar alone.

Blazar Combined With Chappel

The Examiner alleges that the disclosure in Chappel of a thirty minute in vitro incubation step of donor cells with a masking agent when combined with Blazar renders the claimed invention obvious. This allegation is not supported by the cited references.

The invention in Chappel is clearly distinct from the claimed invention. Chappel does not teach inhibiting the B7/CD28 pathway. Chappel does not teach or suggest the ex vivo application of antibodies to B7-1 or B7-2 in a method of transplanting cells. Instead, Chappel teaches masking LFA-1, MHC I, or MHC II. None of the molecules disclosed by Chappel activate T cells via the B7/CD28 co-stimulatory pathway. Thus, Chappel merely suggests the use of a 30 minute in vitro incubation step with reagents that target molecules distinct from the claimed invention.

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A skilled artisan would not be motivated to combine Blazar with Chappel, because a skilled artisan reading Blazar in light of Chappel would perceive no need to do so. Blazar demonstrates that targeting the B7 pathway and a second pathway or mechanism using an in vitro 3-hour incubation step is effective. (*See* Blazar, Figures 1, 5 and 7). Mice treated with CTLA-Ig and anti-LFA-1 in vitro, followed by the same regimen in vivo survived 100 days post bone marrow transplant. (*See* Blazar, Figure 5). In contrast, Chappel's results are far less impressive. Chappel discloses transplanting human pancreatic cells into mice. Chappel suggests pre-incubating the pancreatic cells for 30 minutes with two Fab's specific to MHC I prior to transplant (MHC I is not part of the B7 co-stimulatory pathway). Chappel notes insulin production was sustained for merely 14 days (*See* Chappel Table 1). Thus, Chappel teaches targeting a different mechanism, to achieve less effective results, using a shorter in vitro incubation period. Nothing in Chappel would motivate the skilled artisan to combine its disclosure with Blazar. Motivation to combine two references requires a perceived problem to be solved. *See Winner v. Wang*, 202 F.3d 1340, 1349, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000). A skilled artisan would not perceive any problem which would be solved by combining Chappel with Blazar because there was no apparent disadvantage to the method disclosed by Blazar which could be remedied by combining Blazar with Chappel.

Thus, Chappel does nothing to cure the defect of Blazar alone because it fails, even when combined with Blazar, to teach the desirability of using B7-1 and B7-2

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